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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/663,999 | 09/16/2003 | Kaname Ishibashi | 224436 | 8529 |

23460 7590 10/18/2005

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

| EXAMINER | |
|---|---|
| WHISENANT, ETHAN C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/663,999 | ISHIBASHI ET AL. | |
| | Examiner | Art Unit | |
| | Ethan Whisenant, Ph.D. | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**NON-FINAL ACTION**

**1.** The applicant's Preliminary Amendments filed 16 SEP 03 and 20 MAY 04 have been entered. Following the entry of the Preliminary Amendments, **Claim(s) 16-29** is/are pending.

## SEQUENCE RULES

**2.** This application complies with the sequence rules and the sequences have been entered by the Scientific and Technical Information Center.

## CLAIM OBJECTIONS

**3.** **Claim(s) 23-24 and 27-28** is /are is objected to for the following minor informality.

These claims recite nucleotide sequences without reciting the corresponding SEQ ID NOs. Please correct

## 35 USC § 112 - 1ST PARAGRAPH

**4.** The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

## CLAIM REJECTIONS under 35 USC § 112- 1ST PARAGRAPH

**5.** **Claim(s) 22-29** is/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The examiner was unable to find basis in the specification as

originally filed for the limitation in Claim 22 which reads "287-316 site and the 342-371 site" and the limitation in Claim 26 which reads "176-205 site and the 265-294 site." In addition there is no basis for the oligonucleotide sequences recited in Claims 23-24 and 27-28. They are not present in the Sequence listing.

**35 USC § 103**

**6.** The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**7.** This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

**CLAIM REJECTIONS UNDER 35 USC § 103**

**8.** **Claim(s) 16-18** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer et al. [US 5,728,527 (1993) in view of Graham et al. [US 6,127,120 (2000)].

Singer et al. teach a method of selectively separating live cells which have expressed a specific mRNA from a live cell group comprising all of the limitations recited in Claim 16-17 except these authors do not teach determining a site within the specific mRNA that has high accessibility for oligonucleotide probe hybridization and preparing an oligonucleotide probe, labeled with a fluorescent dye, having a base sequence capable of hybridizing to the base sequence of the thus determined site. However, as evidenced by Grahm et al. it was well known prior to the instant invention that "mRNA has

considerable secondary structure which can be predicted by computer modelling although this method is not satisfactory. Only certain regions of the mRNA are liable to be both single stranded and accessible for binding to an antisense oligonucleotides." Based on these findings, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Singer wherein prior to synthesizing the oligonucleotide probe, the targeted mRNA is modeled via computer to determine the position within the mRNA which is most likely to be amenable to probe hybridization (i.e. determining a site within the specific mRNA that has high accessibility for oligonucleotide probe hybridization) and then based on the modeling results synthesizing the appropriate probe(s).

As regards the limitation present in **Claim 17** note Column 6, beginning at about line 46 wherein Singer et al. teach "The hybridization method can also be performed using energy transfer to detect the hybridization. In this case, two oligonucleotides, one labelled with an energy donor group and one labelled with an energy acceptor group, comprise the probe. The two oligonucleotides can be modified, unmodified or a combination of both. The two oligonucleotides have sequences such that they hybridize to immediately adjacent sites on the target sequence. The oligonucleotide with its 5' end closest to the 3' end of the second oligonucleotide when hybridized to immediately adjacent sites on the target nucleic acid sequence is labelled on the 5' end with either an energy donor group or an energy acceptor group; the second oligonucleotide is labelled on the 3' end with whichever group, either an energy donor group or an energy acceptor group, not used as a label on the first oligonucleotide. When the two oligonucleotides are brought near each other due to hybridization to the target sequence, energy transfer takes place between them. When two fluorophores whose excitation and emission specta overlap are in sufficient close proximity, the excited state energy of the donor molecule is transferred to the neighboring acceptor fluorophore. The result is quenching of donor fluorescence, an enhancement of acceptor fluorescence intensity. The cells are irradiated with light at an excitation wavelength, energy transfer occurs, and the emitted light is detected by increase in fluorescence intensity (see, e.g. Cardullo et al., Proc. Natl. Acad. Sci. USA 85: 8790-8794 (1988))."

As regards the limitation present in **Claim 18** note Column 2, beginning at about line 5 wherein Singer et al. teach "However, hybridization can also be followed by physical segregation of the cells of interest by known methods, such as fluorescence activated cell sorting or microdissection. The isolated subpopulation can then be cultured as a subclone or used as a source of RNA for cDNA library construction."

**9.** **Claim(s) 19-21** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer et al. [US 5,728,527 (1993) in view of Graham et al. [US 6,127,120 (2000)] as applied against Claims 16-18 above and further in view of Levinson [US 6,562,343 (2003)].

Singer et al. teach all of the limitations of Claims 19-21 except these authors do not explicitly teach an embodiment wherein the target mRNA is a cytokine. Niether do these authors teach that the cells separated are TH1 cells or TH2 cells. However, Levinson et al. do teach the identification, separation and isolation of TH1 or TH2 cells based on the difierential expression of certain proteins including cytokines. See for example Column 3, at beginning at about line 61. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Singer et al. wherein mRNA for cytokines and/or other proteins difierentially expressed in TH cell subpopulations is used to isolate a TH cell subpopulation of interest (i.e. TH1 or TH2 cells). The motivation to make this modification comes from Levinson. See, for example Column 3, at beginning at about line 61 wherein Levinson et al. teach : "A primary goal, for both diagnostic and therapeutic reasons, therefore, would be the ability to identify, isolate and/or target members of a particular TH cell subpopulation. The ability to identify those genes which are differentially expressed within and/or among such TH cell subpopulations is required to achieve such a goal. To date, investigations have focused on the expression of a limited number of specific known cytokines and cytokine receptors in the TH cell population. Cytokines, however, exert effects on cell types in addition to specific TH cell subpopulations, i.e., exhibit a variety of pleiotropic effects. It would be beneficial, therefore, to identify reliable markers (e.g., gene sequences) of TH cell subpopulations whose effects are TH cell subpopulation specific, e.g., which, unlike secreted cytokines, are TH cell subpopulation specific." Furthermore, note that Singer et al. teach in Column 2, beginning at about line 1 - line 16 that their procedure "permits the selection of cells or subpopulations of cells based on gene expression or the presence of a target sequence. After hybridization, the cells of interest can be evaluated with respect to other parameters and segregated by methods such as microdissection or flow sorting. The selected cells can be cultured, further characterized or used as a source of RNA for the construction of cDNA libraries."

**Non-Statutory Obviousness-type Double Patenting Rejection**

**10.** The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982);

*In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**11.** **Claim(s) 22-29** is/are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1-2 of U.S. Patent No. 6,872,525. Although the conflicting claims are not identical, they are not patentably distinct from each other.

## CONCLUSION

**12.** **Claim(s) 16-29** is/are rejected and/or objected to for the reason(s) set forth above.

**13.** Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant, Ph.D. whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30AM -5:30PM EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (571) 272-0745.

The Central Fax number for the USPTO is (571) 273-8300. Before faxing any papers, please inform the examiner to avoid lost papers. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

ETHAN WHISENANT
PRIMARY EXAMINER

Art Unit 1634

**Search Notes**

**17 OCT 05**

**Databases searched: USPATFULL, USPG-PUBS and EUROPATFULL via EAST, CAplus, Medline**

Reviewed the parent(s), if any, and any search(es) performed therein : see the BIB data sheet

Reviewed, the search(es), if any, performed by prior examiners

Search terms:

Inventor(s) : e.g. Ishibashi K?/au

Cell$ same isolat$

or

Cell sort$ of FACS

Hybridization

mRNA

FRET

Fluorescen$

(mRNA with secondary structure) same probe$